

# Selective serotonin reuptake inhibitors and pregnancy: A review of maternal, fetal and neonatal risks and benefits

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## Abstract

Depression is common in women of childbearing age. Whereas non-pharmacological interventions are recommended as first line interventions, pharmacological treatment may be required. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants in pregnancy. Ideally, discussion of the risks and benefits of SSRI use in pregnancy should occur prior to pregnancy. The potential risks of psychotropic medications need to be balanced against the risks associated with untreated psychiatric conditions and the discontinuation of necessary medications.

## Keywords

Drugs (medication), high-risk pregnancy, neonatal medicine, clinical pharmacology

## Introduction

Depression is common in women of childbearing age, affecting 7–19% of pregnant women. Approximately one in seven women is treated for depression prior to pregnancy, during pregnancy or after delivery of a liveborn infant. The majority of women who develop mental health problems during pregnancy or in the postnatal period suffer from mild depressive illness, which is often accompanied by an anxiety component. Whereas non-pharmacological interventions such as guided self help therapy, non directive counselling, cognitive behavioural therapy and interpersonal psychotherapy are first line treatments; 1.8–3.8% of pregnant women will require pharmacological treatment. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants in pregnancy. The Royal College of Obstetricians and Gynaecologists and National Institute for Health and Clinical Excellence (NICE) recommend that all women of childbearing age should be made aware of the potential risks of psychotropic medications whilst also stating that these need to be balanced against the risks associated with untreated psychiatric conditions and the discontinuation of necessary medications. Here, we discuss SSRI use in pregnancy and the associated maternal, fetal and neonatal risks.

## What are SSRIs and how do they work?

SSRIs work by selectively inhibiting reuptake of serotonin (5-hydroxytryptamine). Serotonin is a monoamine neurotransmitter, generally thought to regulate emotions and feelings of happiness.<sup>1</sup> SSRIs are the first group of drugs which are selective for one specific neurotransmitter system in the brain. By blocking the reuptake of serotonin in the synaptic space they increase concentration of serotonin at post-synaptic nerve terminal membrane. They have gained popularity due to their effectiveness, minimal side effects and safety profile in overdose. The first SSRI approved by the Food and Drug Administration (FDA) and introduced in the market was fluoxetine (Prozac 1987), which was launched in the UK in 1989. Table 1 lists the most commonly prescribed SSRIs with their initial starting dose and their maximum daily dose.

Recognised side effects include nausea, vomiting, abdominal pain, diarrhoea, sweating, agitation, anxiety, tremor, rash, sexual dysfunction, sedation, cutaneous bleeding disorders, upper gastrointestinal bleeding and drug interactions. Since SSRIs are mainly metabolised by hepatic cytochrome p450 enzymes, this can give rise to unpredictable drug interactions ranging from no effect to intoxication. Therapeutic use of SSRIs, overdose or interactions with other medications can lead

to a potentially life threatening condition, the serotonin syndrome. This condition results from excessive serotonin activity both at central nervous system and peripheral serotonin receptors.<sup>2</sup> Symptoms include diarrhoea, headache, shivering, excessive perspiration, tachycardia, tremor, agitation and confusion. In severe cases it can lead to high fever, seizures and loss of consciousness. Conversely, a decrease in dose or sudden discontinuation can lead to SSRI discontinuation syndrome (previously called SSRI withdrawal syndrome or SSRI cessation syndrome). This includes symptoms of dizziness, insomnia, nervousness, nausea and agitation which can be a cause of transient physical and somatic morbidity. Therefore, it is important to taper down the dose before discontinuing treatment and to educate patients about the possible consequences of sudden cessation of SSRIs. Concerns have been raised about SSRI use and the increased risk of suicide attempts<sup>3</sup> but there are limited data on this risk in pregnancy. A recent Cochrane review<sup>4</sup> recommended that the increased risk of suicide-related outcomes in adolescents and children prescribed SSRIs must be balanced against the risks of untreated depression.

## Maternal risks and benefits of SSRI use

Unrecognised or untreated depressive disorder in pregnancy can have adverse effects on maternal health and can lead to poor self-care, poor nutrition, lack of obstetric care, smoking, alcohol misuse and risk of self-harm, potentially leading to suicide.<sup>5–7</sup> In the most recent confidential enquiry, The Centre for Maternal and Child Enquiries reported that 21% of women who died from suicide in the UK between 2006 and 2008 suffered from severe depressive illness.<sup>8</sup> Women with a past history of psychiatric illness in pregnancy have a 50% risk of recurrence in a future pregnancy. Depression in pregnancy also increases the risk of postnatal depression, which significantly impacts on both mother and her partner, leading to increased partner depression and higher divorce rates.<sup>9</sup>

Cohen et al.<sup>10</sup> examined the risk of relapse of depression during pregnancy when antidepressants were discontinued at conception.

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**Table 1.** Commonly prescribed SSRIs.

Non propriety name	Trade name	Initial dose	Maximum daily dose (od: once daily)
Selective serotonin re-uptake inhibitors			
Citalopram	Cipramil® (Lundbeck)	20 mg od	60 mg od
Escitalopram	Cipralex® (Lundbeck)	10 mg od	20 mg od
Fluoxetine	Prozac® (Lilly)	20 mg od	60 mg od
Fluvoxamine	Faverin® (Abbott)	50 mg od	150 mg bd
Paroxetine	Seroxat® (GSK)	20 mg od	50 mg od
Sertraline	Lustral® (Pfizer)	50 mg od	200 mg od
Combined serotonin and noradrenaline re-uptake inhibitors			
Duloxetine	Cymbalta/Yentreve® (Lilly)	60 mg od	60 mg od
Venlafaxine	Efexor XL® (Wyeth)	75 mg od	375 mg od

They found that 75% ( $n=24$ ) of women relapsed during pregnancy and the majority of relapses occurred in the first trimester. In a larger study, the same authors found that 26% of women who maintained their medications throughout their pregnancy experienced relapse, compared to 68% who discontinued medication.<sup>11</sup> Women with recurrent depressive episodes and a recent episode should be advised that they are more likely to relapse during pregnancy if they discontinue their antidepressants.

There is limited information on other effects of SSRI use on maternal health in pregnancy. A recent paper suggested that the use of antidepressants during pregnancy was significantly associated with increased risk of pregnancy-induced hypertension with or without pre-eclampsia (odds ratio (OR), 1.53; 95% confidence interval (CI), 1.01–2.33). This appears higher than that which could be attributed to their depression or anxiety disorders alone<sup>12</sup> but more research is required to determine if this is of clinical significance.

Some SSRIs have been linked with alterations in cardiovascular parameters including prolongation of the QT interval and arrhythmia. However, there is also some evidence that SSRI exposure is protective in patients with known cardiovascular disease as untreated depression worsens prognosis. There are limited data available on maternal cardiac effects of SSRI exposure in pregnancy.

## Fetal risks of maternal SSRI use

The role of serotonin in the developing foetus is not fully understood. Animal studies have shown that this monoamine can play a role in cardiac and craniofacial morphogenesis,<sup>13–15</sup> therefore any interference in the fetal serotonergic system could have teratogenic effects, especially since SSRIs cross the placenta in substantial amounts.<sup>16</sup> Hendrick et al. found evidence of SSRIs and their metabolites in 87% of umbilical cord blood samples. The levels were lower than those in maternal serum and varied depending on maternal dose and the specific type of SSRI.<sup>17</sup>

In 2005, the US FDA released a statement on paroxetine use in pregnancy,<sup>18</sup> suggesting a 1.5-fold excess of cardiovascular malformations, primarily ventricular and atrial septal defects. In 2007, NICE recommended fluoxetine as the SSRI of choice in pregnancy, however, in 2011 the Medicines and Healthcare products Regulatory Agency warned that fluoxetine may increase the risk of congenital cardiac malformations to a similar degree as paroxetine.

There is conflicting evidence in the literature regarding SSRIs and the risk of congenital malformations. Alwan et al. did not demonstrate an association between SSRI use in pregnancy and major cardiac defects but suggested associations with anencephaly, craniosynostosis and omphalocele.<sup>19</sup> Jimenez-Solem et al.<sup>20</sup> found an increased risk of

congenital cardiac malformations for pregnancies exposed to an SSRI throughout the first trimester (adjusted OR, 2.01; 95% CI, 1.60–2.53). In contrast, when Nordeng et al.<sup>21</sup> examined a large Norwegian cohort of 63,395 women they concluded that exposure to SSRIs during the first trimester was not associated with increased risk of congenital malformations (adjusted OR, 1.22; 95% CI, 0.81–1.84) or cardiovascular malformations (adjusted OR, 1.51; 95% CI, 0.67–3.43). A recent meta-analysis suggested that many papers have emphasised small statistically significant differences with limited clinical significance.<sup>22</sup>

A recent study of 29 fetuses exposed to prenatal SSRIs suggested reduced fetal middle cerebral artery flow resistance and reduced fetal heart rate variability compared to non-exposed fetuses at 36 weeks of gestation.<sup>23</sup> The authors also found increased cord haemoglobin and haematocrit levels in exposed fetuses and suggested a potential relationship with in utero hypoxia. Further work is needed to clarify this issue. A recent large population based cohort study was reassuring, as it found no association between in utero exposure to SSRIs and stillbirth or neonatal death.<sup>24</sup>

The decision to start an SSRI must be individualised to each patient but the current literature does not support withholding necessary antidepressants in the first trimester because of concerns regarding congenital anomaly risks.

## Neonatal risks of maternal SSRI use

Depression in pregnancy increases the risk of premature delivery, low birth weight, miscarriage, growth restriction, low Apgar scores and high neonatal cortisol levels at birth.<sup>25–29</sup> Use of SSRIs in late pregnancy has also been linked to increased risks of prematurity, persistent pulmonary hypertension (PPHN) in the newborn, respiratory distress syndrome, feeding problems, jaundice, endocrine and metabolic and temperature regulation disorders, hypoglycaemia and neonatal convulsions.<sup>30–32</sup> PPHN has been reported twice as commonly in infants prenatally exposed to SSRIs with an adjusted odds ratio 2.1 (95% CI, 1.5–3.0).<sup>33</sup> However, the absolute risk remains small (3 per 1000 liveborn infants compared with the background incidence of 1.2 per 1000). Levinson-Castiel et al. found that neonatal behavioural syndrome (also called poor neonatal adaptation and neonatal abstinence syndrome) occurs in 30% of neonates exposed to SSRIs in utero.<sup>34</sup> The authors suggested that neonates should be monitored for at least 48 h after birth. The Fetus and Newborn Committee of the Canadian Paediatric Society also advise that newborns with late pregnancy exposure to SSRIs should be observed in hospital for at least 48 h.<sup>35</sup>

Yonkers et al. in a prospective cohort study of 2793 pregnant women examined the risk of preterm birth associated with SSRI use in pregnancy. These authors found that use of an SSRI, both with and

without a major depressive episode, was associated with preterm birth.<sup>36</sup> When compared to infants of women with a psychiatric illness but no SSRI use, infants of women exposed to SSRIs had an increased risk of preterm delivery (adjusted OR, 2.68; 95% CI, 1.83–3.93), neonatal hospital admission (adjusted OR, 1.92; 95% CI, 1.39–2.65) and length of hospital stay longer than three days (adjusted OR, 1.93; 95% CI, 1.11–3.36).<sup>29</sup> Conversely, Nordeng et al.<sup>21</sup> found no significant association between in utero SSRI exposure and preterm birth (adjusted OR, 1.21; 95% CI, 0.87–1.69) or low birth weight (adjusted OR, 0.62; 95% CI, 0.33–1.16), thus they concluded that without adjustments for level of maternal depression and various sociodemographic factors, antidepressant use during pregnancy could wrongly be associated with an increased risk of preterm birth.

SSRI excretion in breast milk varies due to differences in lipid solubility, maternal dose and metabolism, the proportion of foremilk to hind milk, which affects milk concentration and the infant's own metabolism.<sup>37</sup> Current data suggest that maternal SSRIs are compatible with breastfeeding and indeed breastfeeding may also ameliorate SSRI withdrawal symptoms.<sup>37,38</sup> Although there is a paucity of data related to long-term neurodevelopmental outcomes after SSRI exposure during lactation, current advice suggests a reassuring safety profile with normal cognitive development.<sup>37</sup> When Gorman et al.<sup>39</sup> compared the breastfeeding outcomes of women exposed to SSRIs compared to non-exposed women they found that those exposed to an SSRI were significantly less likely to initiate breastfeeding even after adjustment for potential confounders. Again, it is difficult to differentiate the effect of maternal depression from the effect of antenatal exposure to SSRIs and further research is required to elucidate this.

## Infant and childhood risks

Infants of depressed mothers display delayed psychologic, cognitive, neurologic and motor development.<sup>40</sup> Interestingly, children's mental and behavioural disorders improve when maternal depression is in remission, especially if treatment is initiated in a timely manner.<sup>41</sup> Nulman et al.<sup>42</sup> showed that the IQs of children exposed to venlafaxine and SSRIs in utero were significantly lower than that of the children of nondepressed mothers. Children exposed to either treated or non-treated maternal depression had consistently, but nonsignificantly, higher rates of most problematic behaviours than the children of non-depressed mothers.<sup>43</sup> Antidepressant dose and duration of use during pregnancy did not predict any cognitive or behavioural outcome. The cumulative incidence of registered psychiatric or neurodevelopmental disorders was 6.9% among offspring exposed to prenatal exposure to SSRIs.<sup>44</sup> It is difficult to differentiate the contribution of SSRI exposure from other confounding factors.

Mothers suffering from depression are more likely to neglect or abuse the foetus and commit neonaticide.<sup>31,45</sup> Colvin et al.<sup>28</sup> reported that live born children exposed to SSRIs in utero were more likely to die within their first year (OR, 1.8; 95% CI, 1.3–2.6) and more likely to require hospital admission before the age of two years (OR, 1.4; 95% CI, 1.3–1.6).

## Future studies

Data on the fetal risks associated with maternal use of SSRI in pregnancy are inconsistent and further research is required. Future studies should focus on fetal and neonatal outcomes and compare different dose effects. The impact of untreated depression on the foetus, neonate and mother needs to be elucidated as it is currently difficult to determine which effects are related to depression alone and which are associated with SSRI use. Prospective studies should assess long-term neurodevelopmental outcome of infants exposed to SSRIs and those exposed to untreated maternal depression.

## Conclusion

There are no randomised controlled studies assessing efficacy and safety of SSRI use in pregnancy, therefore most of the existing evidence comes from observational studies. These can be difficult to interpret due to the presence of confounding factors. It is also challenging to differentiate between the risks and complications of untreated depression compared to the risks of SSRI use.

SSRIs are the most commonly used and best tolerated treatment for depression. They are effective and relatively safe in overdose. Pregnancy does not protect against the occurrence of depression and the likelihood of relapse is very high in untreated women with recurrent illness.<sup>31</sup> Untreated depression in pregnancy is associated with poorer maternal health and less favourable obstetric outcomes. Lack of recognition and prompt appropriate treatment of depression can have tragic consequences. Furthermore, maternal depression adversely affects child development.

When antenatal psychiatric illness is significant enough to necessitate the use of SSRIs, the benefit of therapy needs to be weighed against the potential risk of fetal malformations, primary pulmonary hypertension of the newborn infant and the neonatal behavioural syndrome. Decisions about SSRI use in pregnancy will also be influenced by the severity of maternal illness. The involvement of the multidisciplinary team should enable women and their carers to decide on an individualised care plan, which balances the risks of untreated depression against the uncertain fetal and neonatal risks. Ideally, discussion of the risks and benefits of SSRI use in pregnancy should occur prior to pregnancy. Every woman should be specifically asked about her mental health history at the booking visit and women at increased risk of antenatal and postnatal psychiatric illness should be identified.<sup>46</sup> Appropriate referral to the perinatal mental health team should facilitate the formulation of a clear management plan for optimising the woman's mental health in pregnancy and a decision regarding the need for treatment with antidepressant medication for patients where the benefits outweigh the risks.

## Conflict of interest

None of the authors have any conflict of interest to declare.

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